near infrared radiation, WO 96/17628; Robert A. Snow, et al., Compounds, WO 98/48838].

Dyes are important to enhance signal detection and/or photosensitizing of tissues in optical imaging and phototherapy. Previous studies have shown that certain dyes can localize in tumors and serve as a powerful probe for the detection and treatment of small cancers (D. A. Bellnier et al., Murine pharmacokinetics and antitumor efficacy of the photodynamic sensitizer 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a, *J. Photochem. Photobiol.*, 1993, 20, pp. 55-61; G. A. Wagnieres et al., In vivo fluorescence spectroscopy and imaging for oncological applications, *Photochem. Photobiol.*, 1998, 68, pp. 603-632; J. S. Reynolds et al., Imaging of spontaneous canine mammary tumors using fluorescent contrast agents, *Photochem. Photobiol.*, 1999, 70, pp. 87-94). However, these dyes do not localize preferentially in malignant tissues.

Efforts have been made to improve the specificity of dyes to malignant tissues by conjugating dyes to large biomolecules (A. Pelegrin, et al., Photoimmunodiagnosis with antibody-fluorescein conjugates: in vitro and in vivo preclinical studies, *J. Cell Pharmacol.*, 1992, 3, pp. 141-145; B. Ballou et al., Tumor labeling in vivo using cyanine-conjugated monoclonal antibodies, *Cancer Immunol. Immunother.*, 1995, 41, pp. 257-263; R. Weissleder et al., In vivo imaging of tumors with protease-activated near-infrared fluorescent probes, *Nature Biotech.*, 1999, 17, pp. 375-378; K. Licha et al., New contrast agents for optical imaging: Acid-cleavable conjugates of cyanine dyes with biomolecules, *Proc. SPIE*, 1999, 3600, pp. 29-35). Developing a dye that can combine the roles of tumor-seeking, diagnostic, and therapeutic functions has

been very difficult for several reasons. The dyes currently in use localize in tumors by a non-specific mechanism that usually relies on the lipophilicity of the dye to penetrate the lipid membrane of the cell. These lipophilic dyes require several hours or days to clear from normal tissues, and low tumor-to-normal tissue ratios are usually encountered. Furthermore, combining photodynamic properties with fluorescence emission needed for the imaging of deep tissues requires a molecule that must compromise either the photosensitive effect of the dye or the fluorescence quantum yield. Photosensitivity of phototherapy agents relies on the transfer of energy from the excited state of the agent to surrounding molecules or tissues, while fluorescence emission demands that the excitation energy be emitted in the form of light (T. J. Dougherty et al., Photoradiation therapy II: Cure of animal tumors with hematoporphyrin and light, Journal of National Cancer Institute, 1978, 55, pp. 115-121). Therefore, compounds and compositions that have optimal tumor-targeting ability to provide a highly efficient photosensitive agent for treatment of tumors are needed. Such agents would exhibit enhanced specificity for tumors and would also have excellent photophysical properties for optical detection.

Each of the references previously disclosed is expressly incorporated by reference herein in its entirety.

Summary of the Invention

The invention is directed to a composition for a carbocyanine dye bioconjugate. The bioconjugate consists of three components: 1) a tumor specific agent, 2) a photosensitizer (phototherapy) agent, and 3) a photodiagnostic agent. The inventive bioconjugates use the multiple attachment points of carbocyanine dye structures to incorporate one or more

receptor targeting and/or photosensitive groups in the same molecule. The composition may be used in various biomedical applications.

The invention is also directed to a method for performing a diagnostic and therapeutic procedure by administering an effective amount of the composition of the cyanine dye bioconjugate to an individual. The method may be used in various biomedical applications, such as imaging tumors, targeting tumors with anti-cancer drugs, and performing laser guided surgery.

Brief Description of the Drawings

Fig 1. shows representative structures of the inventive compounds.

Fig. 2 shows images taken at two minutes and 30 minutes post injection of indocyanine green into rats with various tumors.

Fig. 3 shows fluorescent images of a CA20948 tumor bearing rat taken at one and 45 minutes post administration of cytate.

Fig. 4 is a fluorescent image of a CA20948 tumor bearing rat taken at 27 hours post administration of cytate.

Fig. 5 shows fluorescent images of ex-vivo tissues and organs from a CA20948 tumor bearing rat at 27 hours post administration of cytate.

Fig. 6 is a fluorescent image of an AR42-J tumor bearing rat taken at 22 hours post administration of bombesinate.

Detailed Description of the Invention

The invention relates to novel compositions comprising cyanine dyes having a general formula 1